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e) assaying biological activity of the modified product and optionally assaying stability of the modified protein.

#1

100. (Amended) The method according to claim 94 or 99, wherein specific digestion with specific endoproteases and laser desorption mass spectometry is carried out for characterization and localization of the modified amino acids.

#2

104. (Amended) The method according to claim 94 or 99, wherein said chemical modification comprises alkylation or acylation, said chemical modification being conducted while gradually varying at least one of the conditions under which said chemical modification is conducted, said conditions comprising a pH range between a pH of 5.0 and 7.0, time for conducting said modification, and reagent concentrations.

#3

107. (Amended) The method according to claim 94 or 99, wherein the modification is within or in such close proximity to a metal binding center that it effects a feature selected from the group consisting of biological and chemical features.

#4

108. (Amended) The method according to claim 94 or 99, wherein the modification is performed by reversibly denaturing the substrate and adding chelating agent to remove the metal ion, said chelating being conducted in the presence of urea and EDTA.

109. (Amended) The method according to claim 94 or 99, wherein the modification is specific for one type of amino acid or is specific for only one amine-residue in the peptide or protein.

111. (Amended) The method according to claim 94 or 99, wherein said chemical modification comprises disruption of phosphate binding whereby the modification results in said proteins or peptides having at least one of an antagonisitc or cell inhibitory activity.

#5

112. (Amended) A modified signal substance selected from the group consisting of a protein hormone, peptide hormone, growth factor, a haemopoeitic growth factor, an

inteferon, an interleukin and a colony stimulating factor with enhanced biological activity, antagonistic activity or cell inhibitory activity, wherein said signal substance contains a modification within or in such close proximity to a catalytic center that it effects a biological or biochemical feature.

113. (Amended) A modified signal substance being a Zinc binding signal peptide selected from the group consisting of Growth Hormone, prolactin, insulin, and a member of the same (cytokine) superfamily as the IL-3 receptor, said modified substance having an enhanced biological activity, antagonisitc activity or cell inhibitory activity, wherein the modification is within or in such close proximity to a Zinc binding center that the metal binding properties have been changed.

114. (Amended) The substance according to claim 113, wherein the metal ion is within or in such close proximity to a catalytic center that it effects a biological or biochemical feature.

115. (Amended) The substance according to one of claims 112-114, wherein the modification for producing an antagonist is a chemical modification comprising an alkylation, an acylation or molecular biological modification, wherein said molecular biological modification includes a deletion mutation or substitution mutuation.

119 (Amended) The substance according to claim 118, comprising at least one of the following characteristics

a) 0.1 ng of the substance, modified IL-3 inhibits about 50% of 3ng/ml native IL-3;

b) 3 ng/ml of the substance, modified IL-3 suppresses 80-90% thymidine incorporation of 30-100 ng/ml control IL-3;

c) the substance modified IL-3 inhibits control IL-3 by a factor of 10-100.

122. (Amended) A method for preparing a substance according to one of claims 112-114, said method comprising modifying a signal substance by applying a specific chemical modification of selected amino acids to result in at least one feature selected from the group

consisting of enhanced biological activity, enhanced stability, suppressed antigenicity, acquired antagonistic activity, and cell inhibitory activity, said method comprising the steps of

a) gradual chemical modification of the signal substance, followed by

b) monitoring the modification reaction with a mild and sensitive method such as nondenaturing electrophoresis or electrospray mass spectrometry and optionally confirming the overall structural integrity;

c) protease treatment;

d) mass spectrometry;

e) assaying biological activity of the modified product and optionally assaying stability of the modified signal substance.

123. (Amended) The substance according to one of claims 112-114, wherein the concentration of substance required for inhibition is suitable for clinical application, being less than a hundred fold higher than the native substance concentration, said substance optionally further having increased receptor binding capacity.

125. (Amended) A method of obtaining at least inhibition or suppression of a HIV infection wherein the antibody levels are lowered by any of the following steps

a) suppression of antibody production by B-cells, suppression of generation or maturation of B-cells, preferably said B-cells being anti-HIV-antibody producing B-cells, preferably anti-HIV coat-antibody producing B-cells;

b) plasmaphoresis, partial or complete plasma recovery or selective return of serum,

c) *in vitro* removal of antibodies, preferably HIV-reactive antibodies, preferably HIV-envelope reactive antibodie;

d) *in vivo* depletion, preferably with antibodies, preferably against HIV, preferably against the HIV envelope; or

e) leukophoresis.

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127. (Amended) The method according to claim 125, wherein said method comprises application of bi-specific antibodies, said antibodies optionally being directed against at least one of the combinations CD19/CD3 or CD20

128. (Amended) The method according to claim 125, wherein said method comprises application of B-cell apoptose inducing substances or application of TGF-β as inhibitor of B-cell antibody production.

#9

129. (Amended) A method for stimulating stem cell-replication comprising application of a preparation that is a modified signal substance or a modified signal substance being a zinc binding signal peptide, wherein said modified signal substance comprises interleukin 3 or a substance obtainable according to claim 94.

#10

132. (Amended) A method for stimulating stem cell-replication comprising application of a substance obtainable according to the method of claim 94.

See Appendix for changes to claims